December 6, 1999

Dockets Management Branch, Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane, Room 1061, (HFA-305)
Rockville MD 20852

VIA FAX 301 827-6870

RE: Docket No, 99D-2726 ('Guidance on Labeling for Laboratory Tests – Draft Guidance"

Dear Food and Drug Administration:

I am writing in support of your draft of "Guidance on Labeling for Laboratory Tests" as a board certified anatomic and pathologist practicing in a hospital and reference laboratory for the last 17 years. The product information supplied by or available on request from the vendor may lack good information in terms of a valid reference ('normal') range studies or expected values in conditions that the test commonly ordered.

Virtually every laboratory test product information booklet contains the boilerplate statement "Each laboratory should establish its own reference intervals based upon its patient population." Unfortunately, the vendor often provides no study or too small a study for their reference range. Reference range studies require relatively large numbers of relevant non-diseased individuals for each subgroup's reference range. The International Federation of Clinical Chemistry's and the International Committee for Standardization of Hematology's Approved Recommendation on the Theory of Reference Values state "To obtain reliable estimates the number of values should be preferably be at least 120." (Solberg, H.E. Approved Recommendation on the Theory of Reference Values Part 5. J. Clin. Chem. Clin. Biochem. 25, 645-656, 1987.)

The laboratory I practice at is large enough to undertake such studies if there are a limited number of age and sex subgroups. Unfortunately, vendors often fail to do adequate size studies for comparison to our own study, are reluctant to release the full data for statistical comparison, or do not even do their own study. Attached is an example from Beckmann-Coulter's Synchron manual. The LDH study combines only 50 males plus females. This is too small a study and there are differences in LDH between men and women. The CKMB study is not done; it merely cites other literature.

As the number of subgroups increases, it becomes impractical for each laboratory to perform its own study of 120 or more people per age and sex group. As laboratory testing has become much more standardized recently due to CLIA regulation, it is time for the vendors to do thorough studies and make the full data sets available in electronic format to the customer laboratories.

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Similar considerations apply to disease population. It is invaluable for tumor markers to know the relative elevations that occur with a particular vendor's antibody in conditions such a smoking or different types of cancer.

Thank you for drafting this guideline and soliciting comments from those practicing in pathology laboratories.

Sincerely yours,

James M. Thombery, M.D.

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CALCULATIONS

LDH Assay

The system performs all calculations internally to produce the final reported result. SYNCHRON CX4/5 Systems do not calculate the final result for sample dilutions made by the operator. In these cases, the result produced by the instrument must be multiplied by the dilution factor before reporting the final result. SYNCHRON CX4CE/5CE/7 Systems (including the CX DELTA Systems) will calculate the final result for sample dilutions made by the operator when the dilution factor is entered into the system during sample programming.

REPORTING RESULTS

REFERENCE INTERVAL

Each laboratory should establish its own reference intervals based upon its patient population. The values given below are intended to act only as a guide. These intervals were established on the SYNCHRON CX5 at reaction temperatures of both 30% and 37°C. The population included 50 males and females from Southern California.

Table 3. Reference Interval

INTERVAL	SAMPLE TYPE	CONVENTIONAL UNITS	S.I. UNITS
Beckman	Serum or Plasma (37°C)	180 to 325 U/L	3.0 to 5.4 µkat/L
	Serum or Plasma (30°C)	127 to 226 U/L	2.1 to 3.8 µkat/L

INTERVAL	SAMPLE TYPE	CONVENTIONAL UNITS	S.I. UNITS
Laboratory			

Refer to References (4, 5, 6) for guidelines on establishing laboratory reference intervals.

Procedures for reporting results to the appropriate personnel can be found in the HOW TO REPORT RESULTS section of this manual.

Additional reporting Information as designated by this **laboratory:**

PROCEDURAL NOTES

LIMITATIONS

1. If plasma is the sample of choice, the following anticoagulant6 were found to be compatible with this method, based on a study of 20 healthy volunteers:

Table 4. Acceptable Anticoagulants

ANTICOAGULANT	LEVEL TESTED FOR IN VITRO INTERFERENCE	AVERAGE PLASMA-SERUM BIAS* (U/L)
Ammonium Heparin	29 units/mL	NSI
Lithium Heparin	29 units/mL	NSI
Sodium Heparin	29 units/mL	NSI

* NSI = No Significant Interference (within ±30.0 U/L or 7%)

2 The following anticoagulants were found to be incompatible with this method;

Table 5. Incompatible Anticoagulants

ANTICOAGULANT	LEVEL TESTED FOR IN VITRO INTERFERENCE	PLASMA-SERUM BIAS* (U/L)
EDTA	3.0 mg/mL	+89.0
Potassium Oxalate/ Sodium Fluoride	4.0 mg/mL / 5.0 mg/mL	-226.0
Sodium Citrate	6.6 mg/mL	±148.0

* Bias is based on worst case instead of average.
Plus (+) or minus (-) signs in this column signify positive or negative interference.

INTERFERENCES

1. Sample6 showing evidence of hemolysis should not he used. Hemolysis may cause falsely elevated results.
2. Lipemic samples > 3+ should be ultra-centrifuged and the analysis performed on the infranate.
3. Refer to References (7, 8, 9) for other interferences for drugs, disease and preanalytical variables.

Beckman - CKMB Assay

CALCULATIONS

The system performs all calculations internally to produce the final reported result. SYNCHRON CX4/5 Systems do not calculate the final result for sample dilutions made by the operator. In these cases, the result produced by the instrument must be multiplied by the dilution factor before reporting the final result. SYNCHRON CX4CE/5CE/7 Systems (including the GX DELTA Systems) will calculate the final result for sample dilutions made by the operator when the dilution factor is entered into the sysrem during sample programming.

REPORTING RESULTS

REFERENCE INTERVAL

Each laboratory should establish its own reference intervals based upon its patient population. The reference intervals listed below were taken from literature.[7]

Table 2. Reference Interval

INTERVAL	SAMPLE TYPE	CONVENTIONAL UNITS	S.I. UNITS
Literature	Serum or Plasma (37°C)	2.3 to 9.5 U/L	0.04 to 0.16 µkat/L
	Serum or Plasma (30°C)	0.5 to 5.4 U/L	0 to 0.090 µkat/L

INTERVAL	SAMPLE TYPE	CONVENTIONAL UNITS	S.I. UNITS
Laboratory			

Refer to References (4, 8, 9) for guidelines on establishing laboratory reference intervals.

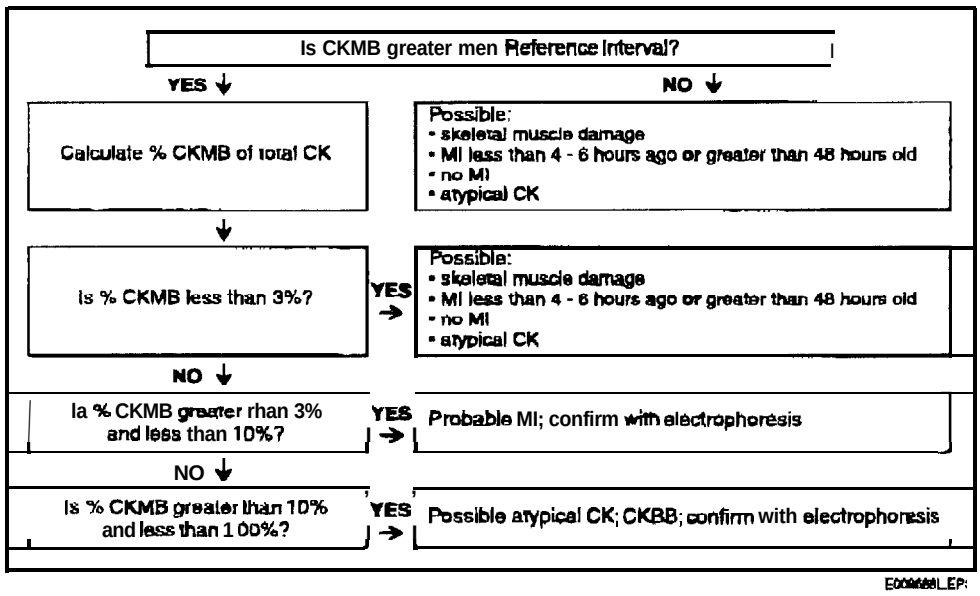

Figure 1.O Interpreting CKMB Results

Procedures for reporting results to the appropriate personnel can be found in the HOW TO REPORT RESULTS section of this manual.

Additional reporting information as designated by this laboratory:

PROCEDURAL NOTES

LIMITATIONS

1. If plasma is the sample of choice, the following anticoagulants were found to be compatible with this method, based on a study of 20 healthy volunteers.

'Table 3. Acceptable Anticoagulants

ANTICOAGULANT	LEVEL TESTED FOR IN VITRO INTERFERENCE	AVERAGE PLASMA-SERUM BIAS' (U/L)
EDTA	3.0 mg/mL	NSI
Lithium Heparin	29 units/mL	NSI
Sodium Citrate	6.8 mg/mL	NSI
Sodium Heparin	29 units/mL	NSI

NSI = No Significant Interference (within ±4.0 U/L or 7%)

2. The following anticoagulants were found to be incompatible with Mis method:

Table 4. Incompatible Anticoagulants

ANTICOAGULANT	LEVEL TESTED FOR IN VITRO INTERFERENCE	PLASMA-SERUM BIAS* (U/L)
Ammonium Heparin	29 units/mL	-4.6
Potassium Oxalate/ Sodium Fluoride	4.0 mg/mL / 5.0 mg/mL	-4.6

Bias is based on worst case instead of average.
*Plus (+) or minus (-) sigm in this column signify positive or negative interference.

3. Any creatine kinase-BB will be expressed as creatine kinase-MB in immunoinhibiiion methods of this type.

NOTE

If creatine kinase-MB Is greater than 10% of total creatine kinase, use an alternative method to confirm results.

4. Creatine kinase-MB variants can be found in disease states other than myocardial infarction.'

5. Specimens with a total CK greater than 1200 U/L should be diluted with a protein based diluent before reassay.